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Sustained Response to Eculizumab in a Patient With COVID-19—Associated Acute Thrombotic Microangiopathy of the Allograft Kidney: A Case Report

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ABSTRACT

Acute thrombotic microangiopathy (TMA) developing in association with SARS-CoV-2 infection is a rare but recognized phenomenon in native kidneys. In the allograft kidney, a diagnosis of TMA has a broad etiologic differential, including antibody-mediated rejection and recurrent and de novo causes of TMA that affect the native kidney. Prior case reports have described plasma exchange or eculizumab use in patients with COVID-19–associated TMA. Herein, we describe the course of a kidney transplant patient with COVID-19–associated TMA with response to eculizumab that was sustained after medication withdrawal and review the literature on COVID-19–associated TMA of the allograft kidney.

ACUTE kidney injury (AKI) is a common finding in hospitalized patients with COVID-19, with a reported incidence varying between 29% and 46% [1]. Among kidney transplant recipients hospitalized with AKI, rates were reported to be similar at 27% to 47% [2,3]. Pathophysiologic drivers of AKI in kidney transplant recipients include cytokine storm, volume depletion, and sepsis with a multiorgan injury which may be related to a reduction in immunosuppression. Kidney biopsy findings in kidney transplant patients with COVID-19 demonstrate a diverse spectrum of injury, with 45% showing acute rejection [4]. Kidney transplant patients who develop SARS-CoV-2 have well-documented sequelae of COVID-19, including an approximately 10% mortality rate and a 1.4% rate of allograft loss [2]. Thrombotic microangiopathy (TMA) is a rare cause of COVID-related AKI. This report describes a patient with COVID-19–associated TMA of the allograft kidney, with a response to eculizumab that remained sustained after medication withdrawal.

CASE REPORT

The patient is a 55-year-old woman with end-stage kidney disease due to IgA nephropathy (IgAN) who underwent a living unrelated donor kidney transplant. She had a low titer donor-specific antibody (DSA) to HLA-DQ2 with a mean fluorescence

intensity of 1136 but negative B- and T-cell flow cytometric crossmatches. Induction was with anti-thymocyte globulin, and maintenance therapy was prednisone, tacrolimus, and mycophenolate; the post-transplant course was relatively uncomplicated. Tacrolimus was switched to cyclosporin because of hair loss. She received 3 doses of the mRNA SARS-CoV-2 vaccine (Pfizer, Inc, New York, NY, United States) at 23, 24, and 30 months after transplant. She was found to be SARS-CoV-2 positive at 25 months on screening antigen test but was minimally symptomatic and recovered without treatment. At 36 months after the transplant, she developed mild upper respiratory symptoms and tested positive for SARS-CoV-2 on a home antigen test. Fatigue, nasal congestion, chills, sore throat, and the cough continued and worsened over 2 weeks, followed by diarrhea and vomiting. She presented to urgent care 18 days after symptom onset and was found to have AKI (creatinine level, 2.87 mg/dL; up from a baseline of 1.28 mg/dL 2 months prior; reference range ≤ 1.20 mg/dL), anemia (hemoglobin, 9.5 g/dL; reference range, 12–16 g/dL), and

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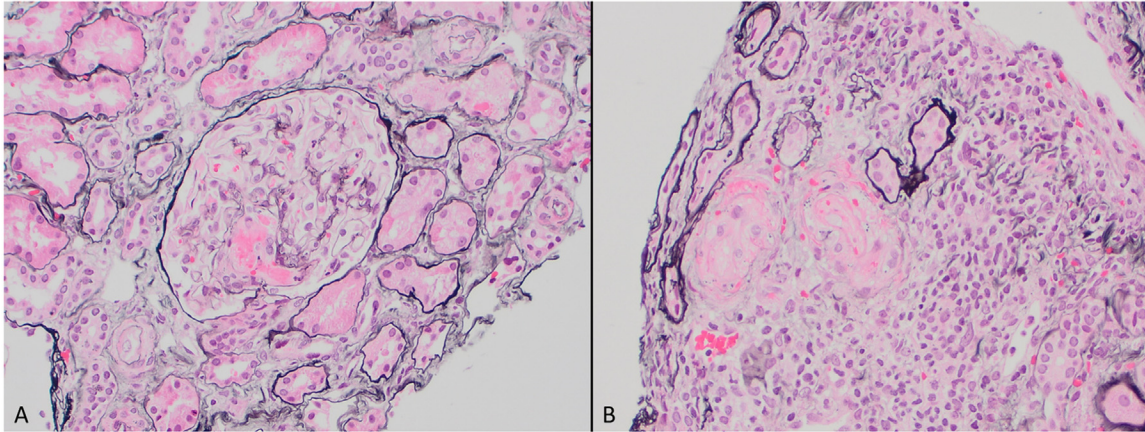


Fig 1. Post-COVID acute thrombotic microangiopathy in a kidney allograft, with (A) glomerular fibrin thrombus and mesangiolysis. There is no glomerulitis; the background tubulointerstitium is without tubulitis, active interstitial inflammation, or peritubular capillaritis (Jones, 200 \times). (B) Arterioles show mucoid intimal edema, red blood cell fragmentation, and fibrin thrombi; arteries were without endotheliitis (Jones, 200 \times).

thrombocytopenia (platelets, $88 \times 10^9/L$; reference range, $140-375 \times 10^9/L$) and was referred for admission.

On arrival, she was hypotensive but responded to intravenous (IV) fluids and remained hemodynamically stable. Urinalysis demonstrated 2+ hematuria and 2+ proteinuria with a urine protein-creatinine ratio of 0.32 mg/mg. She had microangiopathic hemolytic anemia (MAHA) with schistocytes on the peripheral smear. The lactate dehydrogenase (LDH) was elevated (980 U/L; reference range, 115-227 U/L), as was direct bilirubin (0.7 mg/dL; reference range, $0 \leq 0.3$ mg/dL), and haptoglobin was low (<10 mg/dL; reference range, 30-200 mg/dL). A direct Coombs test was negative. Coagulation studies revealed a transient lupus-like inhibitor with subsequently negative antibodies to cardiolipin and β_2 glycoproteins. Cyclosporin levels were within the therapeutic range (124.1 ng/mL; reference range, 100-200 ng/mL), and vitamin B₁₂, methylmalonic acid levels, complement C3, C4, and hepatitis B studies were within normal limits. Creatinine continued to rise, peaking at 4.87 mg/dL, and a kidney biopsy was performed. DSAs were not tested.

Kidney biopsy (Fig 1) contained 30 glomeruli, 3 of which (10%) were globally sclerosed. At least 6 glomeruli (20%) had mesangiolysis and fibrin thrombi. Two foci of arteriolar TMA were seen, with swelling of endothelium, red blood cell fragmentation, and extravasation of red cells. There was no glomerulitis, transplant glomerulopathy, peritubular capillaritis, or C4d staining of peritubular capillaries to suggest antibody-mediated rejection (ABMR). There was no tubulitis, active interstitial inflammation, or arteritis. Immunofluorescence studies were negative for immune complex disease, including recurrent IgAN. There was a background of approximately 50% tubular atrophy and interstitial fibrosis, and moderate to severe arteriosclerosis and arteriolar hyalinosis.

She was treated with eculizumab 900 mg IV weekly $\times 4$ and then 1200 mg IV every 2 weeks. Initially, mycophenolate was held but resumed at discharge and gradually titrated back to baseline doses. A TMA gene panel (Fulgent Genetics, Temple

City, Calif, United States) demonstrated heterozygous mutations of *C9* (c.994C>T p.Pro167Ser) and *CFI* (c.560G>A p.Arg187Gly), which are variants of uncertain significance in domains of possible significance. Over the following 8 months, kidney function and laboratory parameters of MAHA improved steadily (Fig 2), and creatinine level stabilized (1.48 mg/dL) above baseline. Eculizumab therapy was discontinued with continued stable laboratory parameters 2 months later.

DISCUSSION

This report describes a kidney allograft recipient with SARS-CoV-2 infection who developed TMA, which was successfully treated with eculizumab and sustained remission after eculizumab withdrawal. Our observations add to the limited knowledge on the behavior of and associations of COVID-19-associated TMA in the kidney allograft ($n = 6$ including this case, summarized in Table 1) and provide an additional data point on the utility of eculizumab in this setting.

Course of COVID-19 associated TMA in the kidney allograft and response to eculizumab

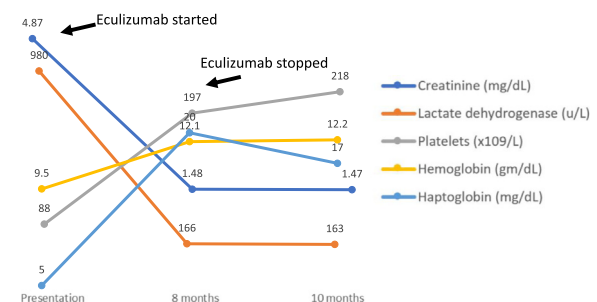


Fig 2. The course of COVID-19-associated thrombotic microangiopathy in the kidney allograft and response to eculizumab. TMA, thrombotic microangiopathy.

Table 1. Summary of COVID-19–Associated TMA in Allograft Kidney

Case Reference	Age, Sex	Prior hx	Symptoms and Laboratory Findings	Kidney Biopsy	Treatment	Follow-up Time	Outcome
Akilesh et al (9)	54, male	ESKD due to HTN, calculi, DD KTx 20 y prior with prior bx showing chronic active ABMR	Acute respiratory failure, fever, nausea, vomiting, AKI, anemia, thrombocytopenia	TMA, glomerular and arteriolar, persistent chronic active ABMR, de novo IgA deposits, severe hyalinosis	MMF held, tacrolimus reduced, low-dose prednisone added	Not provided	Cr to 2.7 mg/dL from 5.2 (baseline 1.9)
Bascunana et al (5)	40s, male	ESKD due to Liddle syndrome, 9 y post transplant, no hx rejection or DSA	1 wk fever, dyspnea, diarrhea, AKI MAHA, pancreatitis, myocardial involvement	Not performed	Plasma exchange with FFP. Immunosuppression discontinued. Antibiotics	1 mo	Cr improved to 1.9 mg/dL from 8.8 (baseline 1.75) normalization of LDH, platelets, haptoglobin
Nizamic et al (8)	49, female	CKD due to FSGS, preemptive DD KTx 3 mo prior, slow graft function, no rejection	Diarrhea, weakness, AKI, MAHA, pancreatitis	Acute TMA. No rejection	Tacrolimus reduced (although troughs in therapeutic range), supportive care	1.5 mo	Cr improved to 1.7 mg/dL from 6.1 (baseline 1.7-2.1). Normalization of Hgb, platelets and improved LDH and lipase
Tarasewicz et al (6)	41, male	ESKD due to IgAN, second KTx 11 mo prior, no DSA	COVID-19 1 mo prior; pneumonia, diarrhea, uncontrolled HTN, AKI, MAHA	Acute TMA, recurrent IgAN, mesangiolytic, proliferative arteriolopathy, no rejection, no IFTA	Plasmapheresis with FFP. Antibiotics. MMF withdrawn, tacrolimus reduced (although troughs in therapeutic range) steroids increased	2 mo	Allograft loss
Casteneda et al (7)	35, female	CKD due to IgA vasculitis, pre-emptive living related ABOi KTx a few days prior	Acute respiratory failure, fever, pneumonia requiring mechanical ventilation	Acute TMA, no rejection	MMF stopped, tacrolimus reduced (although troughs in therapeutic range) Eculizumab loading dose 1200 mg, 900 mg/wk × 4 weeks	1 mo	Cr improved to 1.8 from 3.4 (prior 1.5)
Rehman et al (this report)	55, female	ESKD due to IgAN, LU KTx 3 y prior, no rejection	Mild URI symptoms, diarrhea, vomiting, AKI, MAHA	Acute TMA, moderate IFTA, severe arteriolar hyalinosis, no rejection, no recurrent IgAN	MMF held initially, restarted at discharge. Eculizumab 900 mg IV weekly × 4, 1200 mg IV every 2 wk × 8 mo, then discontinued	10 mo	Cr improved to 1.48 from 4.87 (baseline 1.28). Other laboratory parameters normalized except for haptoglobin

ABMR, antibody mediated rejection; ABOi, ABO incompatible; AKI, acute kidney injury; CKD, chronic kidney disease; Cr, creatinine; DD, deceased donor; DSA, donor specific antibody; ESKD, end-stage kidney disease; FFP, fresh frozen plasma; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; Hx, history; IgAN, IgA nephropathy; KTx, kidney transplant; LDH, lactate dehydrogenase; LU, living unrelated; MAHA: microangiopathic hemolytic anemia; MMF, mycophenolate mofetil; TMA, thrombotic microangiopathy.

In a review of previously reported cases of COVID-19–associated TMA in the kidney allograft, the cause of end-stage kidney disease was IgAN in 3 of 6 patients, and 1 had concurrent recurrent IgAN on biopsy, whereas another had de novo IgAN. COVID-19 symptoms ranged from mild to severe and included upper respiratory and gastrointestinal manifestations. Patients usually had multiple systemic laboratory features of TMA, including elevated lactate dehydrogenase, anemia, thrombocytopenia, low haptoglobin, and/or schistocytes on peripheral smears. Where reported, other viral workups, including serologic studies for cytomegalovirus, parvovirus, Epstein-Barr virus, HIV, hepatitis C virus, and hepatitis B virus, were negative, although 2 patients received antibiotics for presumed superimposed bacterial infection [5,6]. One patient was tested for abnormalities of the complement pathway that showed no pathogenic mutations associated with atypical hemolytic uremic syndrome (aHUS), but heterozygous polymorphisms in *CFH*, *MCP*, and *PLG* were present [7]. Although calcineurin inhibitor toxicity has been associated with TMA, tacrolimus trough levels were within therapeutic range in tested patients [6–8].

Of the 5 with available kidney biopsies, 3 had a significant chronic vascular injury with severe arteriolar hyalinosis [9] or proliferative arteriolopathy in the setting of uncontrolled hypertension [6], whereas 2 were described as acute TMA with a minimal chronic injury. Five of 6 cases occurred without associated rejection or DSA; only 1 occurred in the setting of known chronic active ABMR in a patient with a 20-year-old allograft [9].

In all reported patients, immunosuppressive regimens were reduced in various ways (Table 1). Two previously reported patients were treated with plasma exchange with fresh frozen plasma: 1 had spontaneous improvement with supportive care, and 1 previously reported patient was treated with eculizumab. Despite considerable variation in treatment, 5 of 6 had improved kidney function and/or systemic features of MAHA, with only 1 progressing to allograft loss [6]; however, creatinine level did not return to baseline in any patient.

In summary, based on the current case and review of previously reported patients, COVID-19–associated acute TMA of the kidney allograft has variable symptomatology but may be identified by having at least some characteristic laboratory features of TMA. Most patients do not have concurrent rejection, and acute calcineurin inhibitor toxicity does not play a clear

role in developing this TMA. Preexisting chronic injury, including severe vascular disease, may be seen but is not required for the development of COVID-19–associated allograft TMA. The role of complement-associated genes and the apparent high representation of underlying IgAN in these patients deserves further investigation. Our report currently provides the longest available clinical follow-up (10 months) and demonstrates a stable course after removing eculizumab; more data are needed to determine the overall impact on graft function.

DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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